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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,712	11/15/2000	Juergen Schmitz	830003-2002.1	4820

7590 10/27/2004

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/714,712	SCHMITZ ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *155-159 and 161-179* is/are pending in the application.

4a) Of the above claim(s) *168* is/are withdrawn from consideration.

5)☐ Claim(s) *155,156,158,159,161-167 and 169-171* is/are allowed.

6)☐ Claim(s) *157 and 172-179* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 8/19/04 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendments and remarks filed 8/19/04 have been entered.

2. In view of Applicant's amendment filed 8/19/04, the rejection of Claim 179 under the first paragraph of 35 U.S.C. 112 for the introduction of new matter has been withdrawn.

3. Claims 168 and 172-178 stand withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b) as being drawn to non-elected inventions.

Claims 155-159, 161-167, 169-171, and 179 are being acted upon.

4. Applicant's request for the rejoinder of Claims 168 and 172-178 is acknowledged. Claims 172-178 are drawn to methods depending on allowed product Claim 155. Said claims are hereby rejoined. Claim 168 comprises a product comprising a patentably distinct BDCA-4 antibody. Said claim will not be rejoined.

Accordingly, Claims 155-159, 161-167, and 169-179 are being acted upon.

5. As set forth in the previous actions, Applicant is advised that due to the Office's new electronic application format the Examiner no longer has access to the actual specification and can no longer make informal changes such as updating priority data or correcting minor errors such as mistakes in spelling. Applicant is advised that spelling errors have been noted in the instant specification. Applicant is further advised that all spelling errors must be corrected prior to allowance.

6. As set forth previously, this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Specifically, on the Sequence List filed 7/23/03, SEQ ID NO:2 is identified at line <213> as deriving from mus musculus, whereas

the computer readable copy, also filed 7/23/03, indicates at line <213> that SEQ ID NO:2 is derived from homo sapiens.

Applicant has failed to address this issue. Failure to address this issue in response to this action will be held non-responsive.

7. Applicant has submitted an argument regarding EMBL Accession No. AC006517.

Applicant is advised that no rejection over the sequence is of record, thus, there is no comment regarding the sequence to be made by the Examiner.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 157 stands rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, the recitation of, "The antigen-binding fragment of claim 156 wherein the antibody is human", (Claim 157).

Applicant's arguments, filed 8/19/04, have been fully considered but they are not persuasive. Applicant again argues that Claim 157 is supported by paragraphs 148-149 as well as the prior art. Applicant argues that the specification is enabling. Multiple references have been submitted in support.

A set forth previously, the specification discloses mammalian and humanized mAbs [148], human polyclonal antibodies produced in a mouse [149], murine mAbs [150], and bispecific mAbs [126], but not human mAbs. Regarding the transgenic mice of paragraph 149, said mice comprise only human V-genes, i.e., they do not comprise human H-genes. Thus, said mice could not produce the whole human monoclonal antibodies encompassed by the claims.

Regarding Applicant's assertion of an enabling disclosure, the instant rejection is for lack of adequate written description, not lack of enablement. Regarding the prior art, it is well-established that obviousness in view of the prior art is not the standard for adequate written description, see, for example, *Lockwood v. American Airlines Inc.* 107 F.3d 1565,41 USPQ2d 1961 (Fed. Cir. 1997).

10. The following are new grounds of rejection.

11. Claims 172-179 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) Claim 172, A method for preparing a population of cells enriched for BDCA-2+ cells, comprising contacting a mixture of human cells with an antigen-binding fragment of claim 155 and isolating cells to which the antigen-binding fragment binds.

B) Claim 173, A method of detecting BDCA-2 protein in a biological sample comprising (a) contacting the BDCA-2 protein with the antigen-binding fragment thereof of claim 155 under conditions that permit formation of a complex between the BDCA-2 protein and the antigen-binding fragment; and (b) detecting the formation of the complex.

C) Claim 174, The method of claim 173 wherein the BDCA-2 protein is displayed on the surface of a dendritic cell.

D) Claim 175, The method of claim 174 wherein the step of detecting the formation of the complex comprises detecting at least one metabolic change in the dendritic cell.

E) Claim 176, The method of claim 175 wherein the metabolic change is down-regulation of type I interferon production, down-regulation of Thl immune responses, induction of intracellular Ca2+ mobilization, or polarization of an immune response to Th2.

F) Claim 177, A method of ligating BDCA-2 antigen on a dendritic cell comprising contacting the cell with the antigen-binding fragment of claim 155.

G) Claim 178, A method of screening for agents that interfere with ligation of BDCA-2, said method comprising contacting a BDCA-2 protein and an antigen-binding fragment of

claim 155 in the presence of a test agent and determining whether the test agent reduces binding of the antigen-binding fragment to the protein.

H) Claim 179, A kit comprising an antigen-binding fragment of claim 155 and at least one component selected from the group consisting of: a buffer, a label, a label conjugated to the antigen-binding fragment and a reagent capable of combining with the antigen binding-fragment.

Applicant indicates that no new matter has been added (see the arguments of 11/20/02 and 8/19/04) but no support for the limitations of the claims has been found.

Regarding Claim 172, paragraph 70 comprises a figure legend and not a generic method of preparing a population of cells.

Regarding Claim 173, the cites disclose a method of detecting BDCA-2-expressing DCs or a method employing excess antigen-binding fragment, but not the broader method of the claims.

Regarding Claim 174, paragraph 110 comprises no disclosure of cell surface display of BDCA-2.

Regarding Claim 175, the cites disclose specific cellular reactions to the binding of BDCA-2 with a specific antibody (e.g., AC144), but not the generic method of the claims employing any BDCA-2 antigen-binding fragment.

Regarding Claim 176, see the rejection of Claim 175.

Regarding Claim 177, the cites disclose specific experiments involving the binding of BDCA-2 with a specific antibody (e.g., AC144), but not the generic method of the claims employing any BDCA-2 antigen-binding fragment.

Regarding Claim 178, paragraph 280 discloses only "the screening for suitable moieties for interfering with ligation of BDCA-2", and not the specific method for doing such recited in the claim.

Regarding Claim 179, paragraph 208 discloses a reagent capable of binding with the first reagent [antigen-binding fragment] only *after it has found its target*, which would imply a conformational dependence.

12. Claims 175 and 176 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Regarding novel methods involving biological processes, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)". The MPEP further states that physiological activity can be considered inherently unpredictable.

Given the novelty of BDCA-2 antigen-binding fragments, the specification must be looked to for guidance regarding the possible uses of said antigen-binding fragments. A review of the specification discloses just a single BDCA-2 antigen-binding fragment, the AC144 monoclonal antibody. The specification discloses that said antibody when croslinked can induce intracellular CA2+ and that AC144, employed again with a secondary crosslinking antibody, can reduce the production of type I IFN by plasmacytoid DC in response to a single strain of influenza virus or poly I:C.

This limited disclosure does not provide enablement commensurate with the scope of the claims. First, note that in all cases only the AC144 monoclonal antibody was used and always with an additional cross-linking agent. Thus, the induction of intracellular CA2+ or the reduction of type I IFN production most likely requires said cross-linking as it would not be scientifically logical to include the additional reagent absent its necessity. Additionally, whereas just the single antibody was employed in the specification, the claims encompass the use of *any* BDCA-2 antigen-binding fragments. It is well-known in the art that in many instances antibodies binding the same protein have different effects. For example, certain anti-CD3 antibodies are capable of activation T cells whereas others actually block T cell activation. Finally note that the down-regulation of a Th1 response of the polarization towards a Th2 response, limitations for which the specification provides essentially no enablement, would encompass *in vivo* methods of treatment; the experiments disclosed in the specification are not enabling of any *in vivo* methods.

Accordingly, the limited disclosure of the instant specification is insufficient support for the methods of the instant claims. In view of the quantity of experimentation necessary, the lack of sufficient working examples, the unpredictability of physiological activity, and the lack of sufficient specific guidance in the specification, it would take undue trials and errors to practice the claimed invention.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claim 173 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, specifically, "thereof" in line 2 appears unnecessary.

15. Claim 155-156, 158-159, 161-167, and 169-171 are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

17. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Additionally, the Technology Center receptionist can be reached at (571) 272-1600.

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